Citation:

Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. *Am J Clin Nutr.* 2008 Jun;87(6):1991S-6S.

PubMed ID: 18541600

Study Design:

Systematic Review

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To review the findings of different study designs that evaluate the effects of fish and n-3 fatty acid consumption on fatal coronary heart disease (CHD) and sudden cardiac death (SCD).

Inclusion Criteria:

- Large observational studies
- Randomized clinical trials
- Experimental studies

Exclusion Criteria:

- Ecologic and basic metabolic studies
- Studies that do not evaluate the effects of fish and n-3 fatty acids

Description of Study Protocol:

Recruitment

Literature review; databases searched and search terms not described.

Design: Systematic review

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

Pooled analysis of relative risk of CHD and SCD.

Data Collection Summary:

Timing of Measurements

Varying lengths of study periods.

Dependent Variables

- Coronary heart disease deaths

- Sudden cardiac death
- Clinical events that lead to fatal ventricular arrhythmias, i.e.atherogenesis, acute plaque rupture, CHF, atrial fibrillation, stroke, peripheral artery disease.
- Hemodynamics

Independent Variables

- Dietary factors: types of fish, fats, carbohydrates, nuts, legumes, fruits, vegetables
- Food processing
- Preparation methods
- Supplements, including fish oils

Control Variables

Description of Actual Data Sample:

Initial N:

- Original number of observational studies, randomized clinical trials and experimental studies not described

Attrition (final N):

- 15 observational studies
- 4 randomized clinical trials
- Number of experimental studies not described

Age: not mentioned

Ethnicity: not described

Other relevant demographics:

Anthropometrics

Location:

International studies.

Summary of Results:

Key Findings

- Highest quartile of seafood intake had 60% lower risk of SCD
- Highest quartile of n-3 fatty acid levels had 90% lower risk of SCD
- Modest consumption of oily fish (1-2 servings/wk, or 250 - 500 mg/d of EPA + DHA) had 25-50% lower risk of CHD death
- Lower consumption of n-3 fatty acid (0-250 mg/d of EPA + DHA) had 36% lower risk of CHD death
- Higher levels of marine n-3 fatty acid consumption may modestly reduce nonfatal events
- The stronger effect of modest seafood consumption on risk of CHD and SCD, compared to nonfatal CHD events, suggests that modest consumption of marine n-3 fatty acid more strongly impact fatal cardiac arrhythmias than chronic progression of atherosclerosis or acute plaque rupture.
- There is little further benefit seen at higher intakes.
- Consumption of 2 servings/wk of oily fish reduce mortality by 29%, 2 yr study.
- Fish oil supplementation of 1g/d reduced total mortality by 14%, 3.5 yr study.
- Men with chronic angina, who consumed 2 servings/wk or fish oil 3g/d had no significant effect on mortality during the 9 yr follow-up. In those assigned fish or fish oil, 54% had higher risk of SCD, with a higher risk seen in those assigned fish oil compared to dietary fish advice. Also, higher mortality in both groups assigned fish and fish oil (p=0.08) and a group assigned fruit, vegetables and oats (p=0.07).
- Japanese men and women treated with statins, EPA supplementation (1.8g/d) reduced major coronary events by 19%.
- 3 out 4 randomized clinical trials are concordant with findings in observational studies. Modest n-3 fatty acid

reduces risk of cardiac arrhythmias, higher doses at longer duration may have some benefits for nonfatal CHD events.
- Marmoset monkeys fed diets containing 3.8% energy from fish oil compared to those fed sunflower oil for 16 weeks, reduced the propensity for ventricular fibrillation, $p<0.05$.The monkeys showed a 12.6% to 31.3% increase in myocardial membrane, $p<0.0001$.
- The different effects of fish or fish oil consumption on different cardiovascular outcomes is likely related to varying dose-response and time-responses of the effects on n-3 fatty acids on different cardiovascular risk factors.

Primary vs Secondary Prevention

- 1g/d is recommended for prevention of CHD death in patients with established CHD, however, the evidence does not strongly support a need for a different dose in secondary compared with primary prevention populations.
- Reductions in CHD death with modest fish intake (2 servings/wk) in one secondary prevention trial were similar to the effects seen with fish oil in another secondary prevention trial. These results were similar to findings seen in numerous observational studies. (1-2 servings of oily fish or 250 mg/d EPA + DHA)

Diet Compared to Supplement, EPA or DHA, ALA

- The results of the studies indicate that when using either fish or fish oil the effects on CHD death and SCD are largely related to the marine n-3 fatty acid content.
- Any source of EPA + DHA will provide similar clinical benefits. The choice of fish or fish oil is personal preference.
- The fish or shellfish that contain higher levels of n-3 fatty acids are preferable to maximize benefits.
- The distinct effects of EPA compared to DHA cannot be evaluate in most studies. Some studies suggest that DHA may be more preferentially antiarrhythmic, and DHA tissue levels predict more strongly CHD risk.
- Alpha-linolenic acid (ALA) is the plant n-3 fatty acid. Only a small quantity is converted to EPA and less to DHA.
- The current evidence does not recommend replacing EPA and DHA with ALA as a replacement for seafood.

Contaminants

- The potential cardiovascular benefits outweigh the health risk, in the general population.
- A modest consumption of different seafood varieties (1-3 servings/wk), for the general population, may have a negligible health risk.
- women of childbearing age should limit consumption to 2 servings /wk of fish and other seafood lower in mercury.

Table 1: Observational Studies

Variables	Treatment Group	RR(CI)	P Value	250-500 mg/d EPA+DHA	RR(CI)	P Value	highest quartile of seafood	RR(CI)	P Value	highest quartile of n-3 fatty acid levels	RR
	0 - 250 mg/d EPA+DHA										
SCD(%)	36	0.64, 0.50-0.80	P<0.001	25-50%			60	0.4,0.2-0.7		90	0.1,0.1-0.4
CHD(%)											

* % lower risk

Table 2: Randomized Clinical Trials

Variables	2 servings/wk of oily fish(2 yrs)	p value	fish oil (1g/d) 3.5yrs	p value	oily fish 2 serv/d or 3 g/d fish oil(9yrs)	p value	fish oil (1.8g/d)4.6 yrs	P Value
risk of total mortality(%)(CI)	-29,0.54-0.92	----	-14, 0.76-0.97					

risk of SCD(%)	----	----	-26, 0.58-0.93		54, 1.06-2.23			
risk of CHD(%)	-33%	p<0.01						
risk of coronary events(%)							-19%	p=0.01

Table 3: Experimental Studies

Variable	monkeys eating 3.8% calories from fish oil (baseline)	monkeys eating 3.8% calories from fish oil (follow-up)	p value	monkeys eating 3.8% calories from sunflower oil (baseline)	monkeys eating 3.8% calories from sunflower oil (follow-up)	p value
Ventricular fibrillation(electrical stimulation, during ischemia, during isoproterenol infusion)	reduced		p<0.05			
Myocardial membrane n-3 fatty acid levels(%)	12.6	31.3	p<0.0001			

Author Conclusion:

Observational studies, randomized clinical trials, and experimental studies provide concordant evidence that modest consumption of fish or fish oil (250 mg/d of EPA + DHA, or 1-2 servings/wk) reduces the risk of CHD death and SCD. Together with smoking cessation and regular moderate physical activity, modest consumption of fish or fish oil should be among the first-line treatments for the prevention of CHD death and SCD.

Reviewer Comments:

The author summarized the results from a variety of studies, including observational, randomized clinical trials and experimental studies. There was no consistent way that the results were presented. The populations studied were not always mentioned. The relative risk of CHD deaths and SCD were the major endpoints mentioned, however, other endpoints were mentioned with no statistical information. The study limitations were briefly mentioned in the discussion. The statistical significance that moderate fish or fish oil intake will reduce the risk of CHD death and SCD was weakly presented.

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions

1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	No
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	???
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes